

Cardiac dose-sparing effects of deep-inspiration breath-hold in left breast irradiation

Is IMRT more beneficial than VMAT?

Mazen Sakka^{1,2} · Leonie Kunzelmann¹ · Martin Metzger¹ · Gerhard G. Grabenbauer^{1,2}

Received: 27 March 2017 / Accepted: 31 May 2017 / Published online: 23 June 2017
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Abstract

Background Given the reduction in death from breast cancer, as well as improvements in overall survival, adjuvant radiotherapy is considered the standard treatment for breast cancer. However, left-sided breast irradiation was associated with an increased rate of fatal cardiovascular events due to incidental irradiation of the heart. Recently, considerable efforts have been made to minimize cardiac toxicity of left-sided breast irradiation by new treatment methods such as deep-inspiration breath-hold (DIBH) and new radiation techniques, particularly intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT). The primary aim of this study was to evaluate the effect of DIBH irradiation on cardiac dose compared with free-breathing (FB) irradiation, while the secondary objective was to compare the advantages of IMRT versus VMAT plans in both the FB and the DIBH position for left-sided breast cancer.

Methods In all, 25 consecutive left-sided breast cancer patients underwent CT simulation in the FB and DIBH position. Five patients were excluded with no cardiac displacement following DIBH-CT simulation. The other 20 patients were irradiated in the DIBH position using respiratory gating. Four different treatment plans were generated for each patient, an IMRT and a VMAT plan in the DIBH and in the FB position, respectively. The following parameters were used for plan comparison: dose to the heart,

left anterior descending coronary artery (mean dose, maximum dose, D25% and D45%), ipsilateral, contralateral lung (mean dose, D20%, D30%) and contralateral breast (mean dose). The percentage in dose reduction for organs at risk achieved by DIBH for both IMRT and VMAT plans was calculated and compared for each patient by each treatment plan.

Results DIBH irradiation significantly reduced mean dose to the heart and left anterior descending coronary artery (LADCA) using both IMRT (heart $-20%$; $p = 0.0002$, LADCA $-9%$; $p = 0.001$) and VMAT (heart $-23%$; $p = 0.00003$, LADCA $-16%$; $p = 0.01$) techniques as compared with FB radiation. There were no significant changes in left lung dose by IMRT; however, with VMAT planning, mean dose to the left lung was reduced by $-4%$ ($p = 0.0004$). In addition, DIBH significantly increased the mean dose to the contralateral breast with IMRT ($+14%$, $p = 0.002$) and significantly reduced the dose to the contralateral breast with VMAT planning ($-9%$, $p = 0.003$) compared with the FB position. Additionally, in comparison with VMAT, the IMRT technique reduced mean heart dose both in the FB and the DIBH-position by $-30%$ ($p = 0.0004$) and $-26%$ ($p = 0.002$), respectively. Furthermore, IMRT increased the mean dose to the left lung in both the FB and the DIBH position ($+5%$, $p = 0.003$, $p = 0.006$), respectively. There were no significant changes in dose to the right lung and contralateral breast either in the FB or DIBH position between IMRT and VMAT techniques.

Conclusion Left-sided breast irradiation is best performed in the DIBH position, since a considerable dose sparing to the heart and LADCA can be achieved by using either IMRT or VMAT techniques. A significant additional decrease in heart and LADCA dose by IMRT in both FB and DIBH irradiation was seen compared with VMAT.

✉ Gerhard G. Grabenbauer
gg@diacura.de

¹ Department of Radiation Oncology, Coburg Cancer Center, Ketschendorferstraße 33, 96450 Coburg, Germany

² Faculty of Medicine, Friedrich-Alexander University of Erlangen-Nürnberg, 91054 Erlangen, Germany

Keywords Breast cancer · Breast irradiation · Cardiotoxicity · Intensity modulated radiotherapy · Volumetric modulated arc therapy

Dosisreduktion am Herzen durch tiefe Inspiration bei Bestrahlung der linken Mamma

Ist die IMRT gegenüber der VMAT von Vorteil?

Zusammenfassung

Hintergrund Auf der Basis von Metaanalysen, die eine signifikante Verbesserung der Lokalrezidivraten, aber auch des Überlebens zeigten, gilt die adjuvante Radiotherapie heute als Standardbehandlung nach brusterhaltender Therapie des Mammakarzinoms. Beim linksseitigen Mammakarzinom wurde allerdings eine erhöhte Rate fataler kardiovaskulärer Ereignisse infolge einer Exposition des Herzens mit ionisierender Strahlung ermittelt. Es besteht die Hypothese, dass diese kardiale Toxizität minimiert werden kann, und zwar durch die Bestrahlung in tiefer Inspiration (DIBH) und die Anwendung aktueller Techniken, insbesondere der intensitätsmodulierten Radiotherapie (IMRT) und der volumetrischen Rotationsbestrahlung (VMAT). Primäre Zielsetzung dieser Studie war, beim linksseitigen Mammakarzinom den Effekt der Radiotherapie in tiefer Inspiration auf die Herzbelastung im Vergleich zur freien Atmung zu zeigen. Des Weiteren sollten die Techniken der IMRT und der VMAT mit und ohne tiefe Inspiration verglichen werden.

Methoden Insgesamt 25 konsekutiv eingeschlossene Patientinnen mit einem linksseitigen Mammakarzinom wurden nach brusterhaltender Operation einer CT-Simulation unterzogen. Datensätze in tiefer Inspiration und freier Atmung (Atemmittellage) wurden ermittelt. Fünf Patientinnen wurden wegen fehlender inspirationsabhängiger Beweglichkeit der ventralen Thoraxwand nach DIBH-CT-Stimulation ausgeschlossen. Die übrigen 20 Patientinnen erhielten eine normalfraktionierte Radiotherapie in DIBH-Technik. Für jede Patientin wurden vier verschiedene Bestrahlungspläne generiert, jeweils ein IMRT- und VMAT-Plan in DIBH-Technik und Atemmittellage. Folgende Parameter wurden für den Planvergleich herangezogen: Dosisbelastung von Herz und linker Koronararterie (LADCA; mittlere und maximale Dosis, D25% und D45%), der ipsilateralen und kontralateralen Lunge (mittlere Dosis, D20%, D30%) sowie der kontralateralen Mamma (mittlere Dosis). Die prozentualen Dosisreduktionen an den Risikoorganen infolge der DIBH-Technik wurden sowohl für IMRT- als auch für VMAT-Pläne kalkuliert und für jede individuelle Patientin zwischen den einzelnen Plänen verglichen.

Ergebnisse Die DIBH-Bestrahlung führte zu einer signifikanten Reduktion der mittleren Dosis an Herz und LADCA, sowohl mit der IMRT- (Herz -20% , $p = 0,0002$; LADCA -9% , $p = 0,001$) als auch mit der VMAT-Technik (Herz

-23% , $p = 0,00003$; LADCA -16% , $p = 0,01$) im Vergleich zur Bestrahlung in Atemmittellage. Die Dosis an der linken Lunge war durch die IMRT nicht signifikant verändert, bei VMAT-Planung war die mittlere Dosis jedoch um -4% reduziert ($p = 0,0004$). Zusätzlich wurde infolge der DIBH-Bestrahlung im Vergleich zur Atemmittellage eine signifikant höhere Dosis an der kontralateralen Mamma mit der IMRT ($+14\%$, $p = 0,002$) gesehen, nach VMAT-Planung war die Dosis an der kontralateralen Brust signifikant verringert (-9% , $p = 0,003$). Zusätzlich reduzierte die IMRT-Technik im Vergleich zur VMAT die mittlere Herzdosis sowohl in Atemmittellage als auch nach DIBH-Positionierung um -30% ($p = 0,0004$) und -26% ($p = 0,002$). Im Vergleich zur VMAT führte die IMRT zu einer Dosiserhöhung an der linken Lunge, und zwar in Atemmittellage und DIBH-Position ($+5\%$, $p = 0,003$, $p = 0,006$). Die Dosis an der rechten Lunge und kontralateralen Mamma unterschied sich zwischen IMRT- und VMAT-Technik nicht, weder bei Atemmittellage noch bei DIBH-Positionierung.

Schlussfolgerung Die Bestrahlung des linksseitigen Mammakarzinoms erfolgt am besten mithilfe der DIBH-Technik, zumal mit der IMRT wie auch mit der VMAT eine erhebliche Dosisreduktion an Herz und Koronararterien erreicht werden kann. Die IMRT kann im Vergleich zur VMAT-Bestrahlung eine zusätzliche Dosisreduktion an den genannten Risikoorganen sowohl in DIBH-Technik als auch in Atemmittellage erzielen.

Schlüsselwörter Mammakarzinom · Brustbestrahlung · Kardiotoxizität · Intensitätsmodulierte Radiotherapie · Volumetrische Rotationsbestrahlung

Background

Breast cancer is the most common cancer among women worldwide. Adjuvant radiotherapy is considered the standard management for early-stage breast cancer after breast-conserving surgery. Numerous randomized trials have demonstrated both a reduction in recurrence rates and death rates from breast cancer, as well as improvements in overall survival with adjuvant radiotherapy [1, 2]. However, this advantage following adjuvant radiotherapy is theoretically hampered by an increment in treatment-related mortality that is mainly due to heart disease and lung cancer [3, 4]. Long-term follow-up data after adjuvant radiotherapy have shown increasing risks of ischemic heart disease, presumably due to incidental irradiation of the heart. Particularly left-sided breast cancer radiotherapy was clearly associated with an increased rate of fatal cardiovascular events [4–6]. Part of the anterior heart and the left anterior descending artery (LADCA) will almost invariably receive a signifi-

cant dose during irradiation of the left-sided breast. This may be the cause of myocardial or coronary artery disease. Darby et al. have reported a proportional increase in the rate of major coronary events with the mean cardiac dose per Gy, and showed that the rates of major coronary events increased by 7.4% per Gy. Additionally, the same study indicated that a reduction in radiation dose to the heart decreased the incidence of ischemic heart disease among breast cancer patients [7].

In order to minimize the cardiac toxicity of left-sided breast irradiation, it seems logical to contemplate modern treatment techniques that may reduce the dose to the heart. Recently, considerable efforts have been made using the deep-inspiration breath-hold (DIBH) position for this purpose. The heart moves posteriorly and inferiorly during deep inspiration due to lung expansion and diaphragmatic movements, which maximizes the distance between chest wall and heart in the deep-inspiration position. Radiation is delivered only at deep inspiration in order to reduce the heart volume that receives a high dose, while on the other hand the relative volume of the irradiated ipsilateral lung also decreases. Several dose planning and clinical studies have demonstrated a reduction in dose to the heart and lungs using the DIBH radiation position [8, 9]. However, modern irradiation techniques such as intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) were also involved in left-sided breast irradiation to minimize the irradiation of cardiac structures and the ipsilateral lung without compromising the target coverage.

Recently, IMRT has been increasingly and widely used for the treatment of breast carcinoma, which produced a preferred dose distribution compared to three-dimensional (3D) conformal radiation after conservative surgery, as well as a reduced radiation dose to the adjacent normal organs, especially the heart, in patients with left-sided breast cancer [10–14]. VMAT is a novel radiation technique developed in 2007, which can achieve highly conformal dose distributions, improve target volume coverage and at the same time spare normal tissue by the simultaneous variation of the gantry rotation speed, treatment field shape using the movement of MLC leaves and dose rate during radiation delivery. As an advantage over the IMRT technique, VMAT may additionally reduce individual treatment time. VMAT has been studied and involved in the irradiation of different sites [15–18]. Swamy et al. studied the feasibility of the VMAT radiation technique during DIBH for locally advanced left-sided breast cancer patients, and reported a significant reduction in the heart and lung dose compared to free-breathing (FB) [18].

The primary aim of the study was to evaluate the effect of DIBH irradiation on cardiac dose deposition compared to FB irradiation, while the secondary objective was to com-

pare the advantages of IMRT versus VMAT plans in both the FB and DIBH position for left-sided breast cancer.

Patients and methods

Patients

Between January 2015 and May 2015, a total of 116 female patients with breast cancer or ductal carcinoma in situ (DCIS) were referred to our institution for postoperative radiotherapy after breast-conserving surgery; of these patients, 64 had left-sided tumors. Only patients with good performance status, aged younger than 70 years and a satisfactory understanding of the procedure and who could reproduce a breath-holding status were selected (See CONSORT diagram, Fig. 1). Ultimately, 25 consecutive patients diagnosed with left-sided ductal carcinoma in situ or invasive breast cancer who underwent breast-conserving surgery followed by adjuvant radiotherapy at our institution were included in this planning study. All patients had two CT simulation procedures in the same treatment position, FB and DIBH CT simulation. Five patients were excluded due to no difference in cardiac distance between FB and DIBH CT simulation (Fig. 2). The remaining 20 patients were irradiated in the DIBH position using respiratory gating with

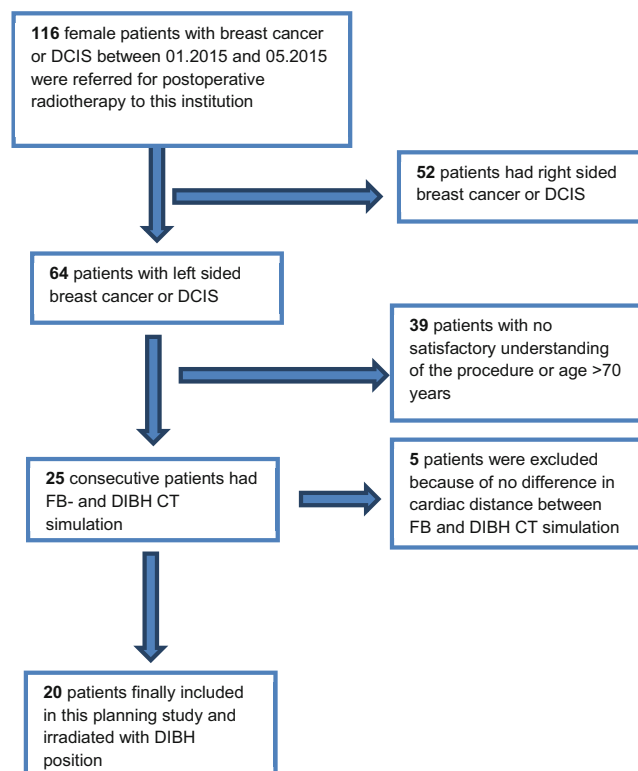


Fig. 1 CONSORT diagram displaying patient selection of 20 consecutive patients with left-sided breast cancer for radiation treatment with the deep-inspiration breath-hold technique

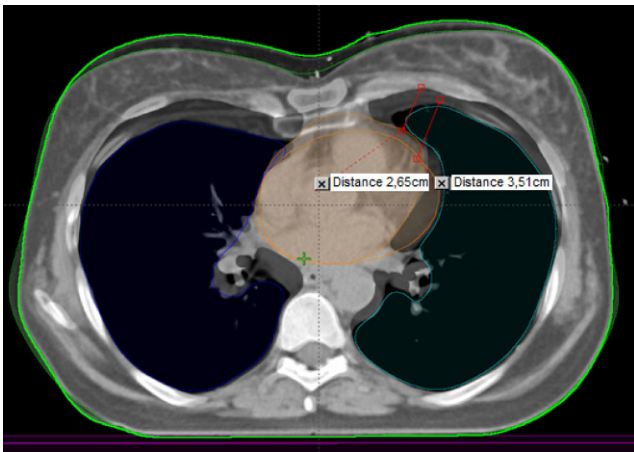


Fig. 2 Difference in cardiac distance between the two CT simulations in the free-breathing and deep-inspiration breath-hold position in a left-sided breast cancer case

whole breast radiotherapy without regional lymph nodes and were retrospectively analyzed. Tumor bed boost was not included in our current analysis.

CT simulation and respiratory gating system

Patients were placed in supine position and immobilized using a knee-fix and carbon fiber customized breast board (Additec, Markt Indersdorf, Germany) with both arms above the head and a copper wire around the breast tissue as an additional way to define the planning target volume (PTV). The CT simulation was performed twice in the FB and DIBH position using a slice thickness of 3 mm from the upper border of the hyoid bone to the diaphragm (Fig. 2). Radio-opaque markers were used during the CT simulation to guide the isocenter shift. After the CT simulation was performed, the digital imaging and communication in medicine (DICOM) images were transferred to the Eclipse (version 13.6, Varian Medical Systems, Palo Alto, CA) treatment planning system (TPS).

The Varian Real-time Position Management respiratory gating system (Varian Medical Systems, Palo Alto, CA) was utilized for the respiratory gating. Patients were trained how to breathe and how to hold their breath before CT simulation and the first radiation.

In order to reproduce the same treatment position during daily radiation fractions, an infrared reflecting marker was placed over the patient's xiphoid process and marked on the patients' skin; a camera was used to detect chest wall movement by following the anterior-posterior motion of the marker. The patients were instructed via microphone on DIBH (maximum 20–30 s) and when to breathe normally.

Delineation of target volumes and organs at risk

The delineation of target volumes and organs at risk (OAR) was performed according to the Radiation Therapy Oncology Group (RTOG) and Danish Breast Cancer Cooperative Group (DBCG) delineation guidelines for adjuvant radiotherapy of early breast cancer [19, 20].

The clinical target volume (CTV) of the breast included all mammary glandular tissue: the lateral border of the breast was defined as the small axillary vessels, while the inferior edge of the clavicle was the cranial border, and the lateral edge of the sternum determined the medial borders of the CTV. The caudal border situated 5–7 mm inferior to the breast fold. A PTV was created by expanding the CTV with adequate distance; however, to avoid high-dose levels in the build-up regions, PTV was retracted 3 mm from the body contour. The contralateral breast was also contoured with the same borders mentioned above. As for OAR, delineation of the heart was defined by the heart muscle and pericardia completely cranial to the lower part of the pulmonary trunk to the apex.

The delineation of the LADCA was feasible using the planning CT without contrast agent, even though visualization of LADCA was not reliable in some slices; therefore, the LAD region was contoured instead of the LADCA by following the anatomic borders (anterior border: pericardium, superior border: the origin of the LADCA from the left main coronary artery and following the anterior-interventricular groove, caudal border: apex cordis). However, in some slices, the LADCA was inferred along the interventricular groove, then interpolated between slices [21]. Auto-contouring was used for the body and both lungs.

Treatment planning

Target volumes and OAR were delineated in both CT simulation data sets for all 20 patients. For each patient, four different treatment planning procedures were performed, IMRT as well as VMAT plans in both the DIBH and the FB position, respectively, in order to evaluate the effect of DIBH on cardiac dose and to compare between IMRT and VMAT techniques. The IMRT treatment plans were generated by the Pinnacle planning system (Version 9; Philips Medical Systems, N.A., Bothell, Washington), then transferred to the Eclipse planning system (version 13.6, Varian Medical Systems, Palo Alto, CA) to be calculated and optimized, while the VMAT treatment plans were directly generated and calculated using the same Eclipse planning system. In addition, 6 MV photon beams were used exclusively to assure adequate comparison between the two treatment techniques. A total dose of 50.4 Gy (specified to D50) with a daily fraction size of 1.8 Gy was prescribed. The tumor bed boost was not included in our current anal-

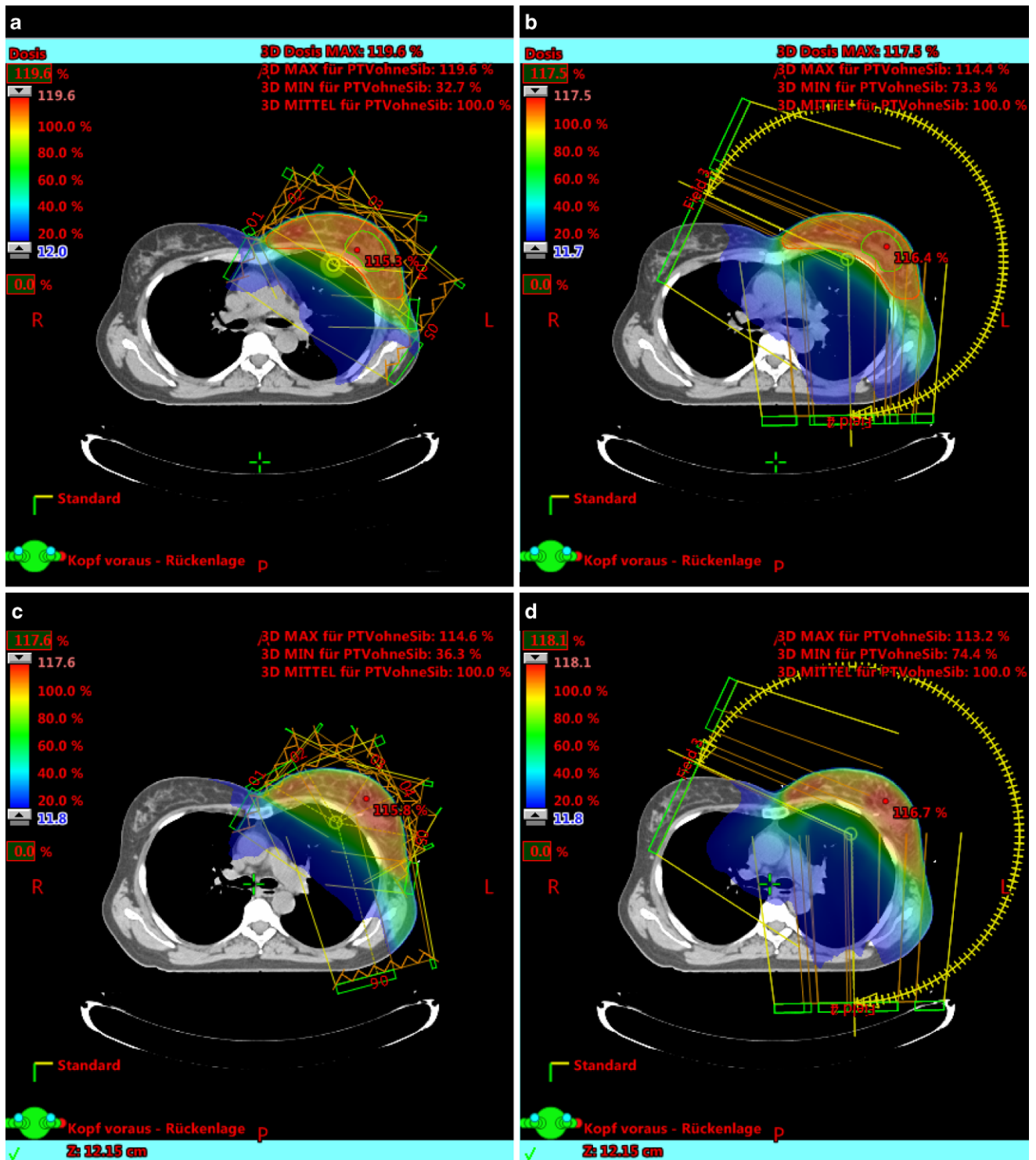


Fig. 3 Beam arrangement and isodose distribution of both VMAT and IMRT plans for a left-sided breast cancer case. **a** IMRT plan in the free-breathing (FB) position, **b** IMRT plan in the deep-inspiration breath-hold (DIBH) position, **c** VMAT plan in the FB position and **d** VMAT plan in the DIBH position

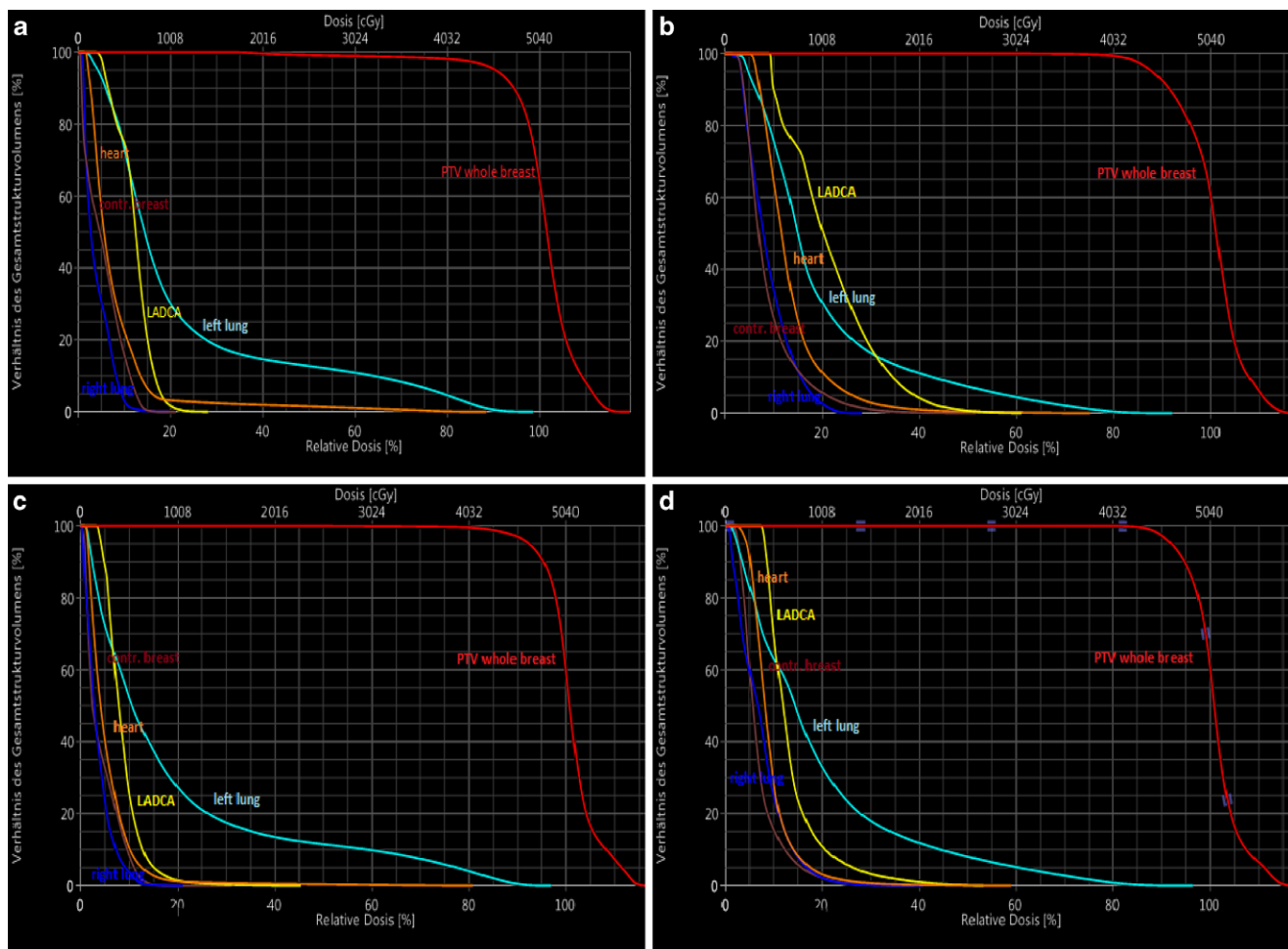


Fig. 4 Dose volume histograms (DVH) of target volume and OAR. **a** FB position IMRT plan, **b** FB position VMAT plan, **c** DIBH position IMRT plan and **d** DIBH position VMAT plan

ysis. Treatment plans with IMRT and VMAT were optimized to achieve 95% coverage of the prescribed dose to the PTV (whole breast). IMRT plans were performed with 5–7 beams with different gantry angles, which were optimized to achieve the prescribed doses to the PTV, while at the same time sparing the OAR using inverse planning optimization with a dose volume optimizer and an analytical anisotropic algorithm (AAA) for dose calculation. A leaf motion calculator was used to calculate leaf motions. VMAT plans were generated with four semi-arcs and created with inverse planning optimization with a progressive resolution optimizer (PRO) and AAA for dose calculation.

Dose constraints were given specifically by each plan to reach the optimal plan, which was evaluated using dose volume histograms. Fig. 3 presents a typical isodose distribution and beam arrangement of both VMAT and IMRT plans for a case of left-sided breast cancer in the FB and DIBH position.

Dosimetric assessment

Different doses from the dose-volume histograms (DVH) for heart, LADCA, lungs and contralateral breast were extracted and compared between the DIBH and FB position for each IMRT and VMAT plan. Fig. 4 shows the DVH of target volume and OAR for IMRT and VMAT plans in the FB and DIBH position for the same case as above.

Statistical analysis

The Wilcoxon signed rank test was used to compare doses and volume differences, while the data were analyzed by SPSS Statistics software (version 22.0, IBM). The results were considered statistically significant at a *p*-value of <0.05 for all tests.

Results

For each treatment plan, several doses to OAR were obtained from the DVH and compared for both IMRT and VMAT plans in the DIBH and the FB position, respectively. The principal parameters included: mean heart dose, maximum heart dose, D25% and D45% to the heart, mean dose, maximum dose and D25% to the LADCA, mean dose, D20%, D30% to the ipsilateral lung, mean dose, D20%, D30% to the contralateral lung and mean dose to the contralateral breast. Dose reduction differences in percentages for all OAR achieved by the DIBH position as compared to FB for both VMAT and IMRT plans were calculated for each patient and each treatment plan, respectively.

Comparison of DIBH versus FB

Dose to heart and LADCA

Mean values for total dose to the heart and LADCA following IMRT and VMAT planning in the DIBH and FB positions are listed in Tables 1 and 2. A significant reduction in total heart and LADCA dose in the DIBH position compared with the FB position by both techniques, IMRT and VMAT, was demonstrated. For IMRT planning, the heart parameters showed a reduction in Dmax of 39% ($p < 0.01$), in Dmean of 20% ($p = 0.0002$), in D25% of 13% ($p = 0.0001$), in D45% of 15% ($p = 0.00001$); the dose parameters to the LADCA showed a reduction in Dmax of 18% ($p = 0.02$), in Dmean of 9% ($p = 0.001$) and in D25% of 10% ($p = 0.003$). Following VMAT planning, the respective parameters for reduced heart dose were 29% ($p = 0.004$), 23% ($p = 0.00003$), 21% ($p = 0.0001$) and 22% ($p =$

Table 1 Overview of the average dose to the heart in Gy following IMRT and VMAT planning in deep-inspiration breath-hold (DIBH) and free-breathing (FB)

Heart dose	FB-IMRT	DIBH-IMRT	DIBH vs FB with IMRT	<i>P</i> value	FB-VMAT	DIBH-VMAT	DIBH vs FB with VMAT	<i>P</i> value
Dmax	38.95 ±7.40	23.44 ±12.43	-15.51 (39%)	0.01	29.82 ±7.73	20.90 ±6.82	-8.91 (29%)	0.004
Dmean	3.71 ±0.70	2.96 ±0.61	-0.74 (20%)	0.0002	5.3 ±1.10	4.03 ±0.74	-1.27 (23%)	0.00003
D25%	4.42 ±0.73	3.84 ±0.69	-0.58 (13%)	0.0001	6.14 ±1.23	4.81 ±0.81	-1.32 (21%)	0.0001
D45%	3.18 ±0.71	2.68 ±0.69	-0.50 (15%)	0.00001	4.92 ±0.95	3.81 0.63	-1.10 (22%)	0.0001

Table 2 Overview of average dose (in Gy) to the left anterior descending coronary artery (LADCA) following IMRT and VMAT planning in deep-inspiration breath-hold (DIBH) and free-breathing (FB)

LADCA dose	FB-IMRT	DIBH-IMRT	DIBH vs FB with IMRT	<i>P</i> value	FB-VMAT	DIBH-VMAT	DIBH vs FB with VMAT	<i>P</i> value
Dmax	14.93 ±3.94	12.28 ±3.49	-2.65 (18%)	0.02	21.15 ±6.3	15.45 ±5.6	-5.7 (27%)	0.001
Dmean	6.40 ±0.88	5.80 ±0.68	-0.59 (9%)	0.001	8.72 ±1.76	7.31 ±0.97	-1.40 (16%)	0.01
V25	7.33 ±0.55	6.58 ±0.68	-0.75 (10%)	0.003	10.32 ±2.32	8.48 ±1.18	-1.84 (18%)	0.01

Table 3 Overview of average dose to the ipsilateral lung following IMRT and VMAT planning in deep-inspiration breath-hold (DIBH) and free-breathing (FB)

Left lung dose	FB-IMRT	DIBH-IMRT	DIBH vs FB with IMRT	<i>P</i> value	FB-VMAT	DIBH-VMAT	DIBH vs FB with VMAT	<i>P</i> value
Dmean	10.79 ±0.89	10.42 ±0.71	-0.37 (3%)	0.1	10.27 ±1.06	9.89 ±1.03	-0.38 (4%)	0.0004
D20%	14.46 ±0.92	14.19 ±0.88	-0.38 (4%)	0.6	13.62 ±1.22	13.96 ±1.49	+0.33 (2%)	0.003
D30%	10.69 ±0.96	10.45 ±0.82	-0.25 (2%)	0.06	10.69 ±1.04	10.96 ±1.27	+0.27 (3%)	0.001

0.0001), and the respective data for reduced LADCA dose were 27% ($p = 0.001$), 16% ($p = 0.01$) and 18% ($p = 0.01$).

Dose to ipsi- and contralateral lungs

There were no significant differences between FB and DIBH position of the left lung dose following IMRT planning. However, with VMAT planning, the mean dose to the ipsilateral lung was slightly reduced by 4% ($p = 0.0004$), while D20% and D30% were increased by 2% ($p = 0.003$) and 3% ($p = 0.001$), respectively (Table 3). On the other hand, the DIBH position significantly reduced Dmean and D30% to the right lung. Following IMRT planning, these parameters experienced a reduction of 2% ($p = 0.04$) and 1% ($p = 0.03$), respectively. After VMAT planning, Dmean, D20% and D30% to the contralateral lung were reduced by 17% ($p = 0.00007$), 11% ($p = 0.001$) and 13% ($p = 0.001$), respectively (Table 4).

Dose to contralateral breast

The DIBH position significantly increased the contralateral breast dose by IMRT compared to the FB position 14%

($p = 0.002$). Following VMAT-planning, mean dose to the contralateral breast was lowered by 9% ($p = 0.003$) with the DIBH as compared to the FB position (Table 5).

Comparison of IMRT versus VMAT

Dose to heart and LADCA

A significant dose reduction was found for the heart with IMRT planning as compared with VMAT planning based on FB as well as on DIBH positioning (Table 6). The IMRT technique reduced the mean heart dose, D25% and D45% by 30% ($p = 0.0004$), 28% ($p = 0.0003$) and 35% ($p = 0.001$), respectively in the FB position. This significant reduction using the IMRT technique was also noted in the DIBH position with a reduction in the mean heart dose, D25% and D45% of 26% ($p = 0.002$), 20% ($p = 0.002$) and 29% ($p = 0.003$), respectively.

As for the LAD region, an average dose reduction was achieved with IMRT technique in both the FB and DIBH position, albeit being statistically significant only for the DIBH position. Dmax, Dmean and D25% to the LADCA was lowered by 20% ($p = 0.003$), 20% ($p = 0.03$) and 22%

Table 4 Overview of average dose to the contralateral lung (in Gy) following IMRT and VMAT planning in deep-inspiration breath-hold (DIBH) and free-breathing (FB)

Right lung dose	FB-IMRT	DIBH-IMRT	DIBH vs FB with IMRT	P value	FB-VMAT	DIBH-VMAT	DIBH vs FB with VMAT	P value
Dmean	2.01 ±0.45	1.97 ±0.32	-0.04 (2%)	0.9	4.28 ±0.84	3.53 ±0.56	-0.75 (17%)	0.00007
D20%	3.14 ±0.74	3.07 ±0.42	-0.07 (2%)	0.9	6.04 ±1.1	5.32 ±0.72	-0.72 (11%)	0.001
D30%	2.56 ±0.65	2.53 ±0.42	-0.03 (1%)	0.5	5.15 ±0.91	4.49 0.61	-0.67 (13%)	0.001

Table 5 Mean dose to the contralateral breast following IMRT and VMAT planning in deep-inspiration breath-hold (DIBH) and free-breathing (FB)

Contr. Breast dose	FB-IMRT	DIBH-IMRT	DIBH vs FB with IMRT	P value	FB-VMAT	DIBH-VMAT	DIBH vs FB with VMAT	P value
Dmean	1.51 ±0.64	1.77 ±0.72	+0.26 (14%)	0.002	3.59 ±0.94	3.27 ±0.57	-0.32 (9%)	0.003

Table 6 Overview of the average heart dose comparing IMRT vs VMAT both in the free-breathing (FB) and deep-inspiration breath-hold techniques (DIBH)

Heart dose	FB-IMRT	FB-VMAT	IMRT vs VMAT with FB	P value	DIBH-IMRT	DIBH-VMAT	IMRT vs VMAT with DIBH	P value
Dmean	3.71 ±0.70	5.3 ±1.10	-1.59 (30%)	0.0004	2.96 ±0.61	4.03 ±0.74	-1.07 (26%)	0.002
D25%	4.42 ±0.73	6.14 ±1.23	-1.72 (28%)	0.0003	3.84 ±0.69	4.81 ±0.81	-0.97 (20%)	0.002
D45%	3.18 ±0.71	4.92 ±0.95	-1.74 (35%)	0.001	2.68 ±0.69	3.81 0.63	-1.13 (29%)	0.003

Table 7 Overview of the average dose to the left anterior descending coronary artery (LADCA) comparing IMRT vs VMAT using both the free-breathing (FB) and deep-inspiration breath-hold techniques (DIBH)

LADCA dose	FB-IMRT	FB-VMAT	IMRT vs VMAT with FB	<i>P</i> value	DIBH-IMRT	DIBH-VMAT	IMRT vs VMAT with DIBH	<i>P</i> value
Dmax	14.93 ±3.94	21.15 ±6.3	-6.22 (29%)	0.09	12.28 ±3.49	15.45 ±5.6	-3.17 (20%)	0.003
Dmean	6.40 ±0.88	8.72 ±1.76	-2.32 (26%)	0.1	5.80 ±0.68	7.31 ±0.97	-1.51 (20%)	0.03
D25%	7.33 ±0.55	10.32 ±2.32	-2.99 (28%)	0.07	6.58 ±0.68	8.48 ±1.18	-1.9 (22%)	0.01

Table 8 Average dose to the ipsilateral lung comparing IMRT vs VMAT both in free-breathing (FB) and deep-inspiration breath-hold techniques (DIBH)

Left Lung	FB-IMRT	FB-VMAT	IMRT vs VMAT with FB	<i>P</i> value	DIBH-IMRT	DIBH-VMAT	IMRT vs VMAT with DIBH	<i>P</i> value
Dmean	10.79 ±0.89	10.27 ±1.06	+0.52 (5%)	0.003	10.42 ±0.71	9.89 ±1.03	+0.53 (5%)	0.006

($p = 0.01$), respectively, when using IMRT compared with the VMAT plan in the same position (Table 7).

Dose to ipsilateral and contralateral lungs

The mean dose to the left lung with the IMRT technique was slightly but significantly increased both with the FB and the DIBH position by 5% ($p = 0.003$) and 5% ($p = 0.006$), respectively (Table 8). However, there were no significant differences in dose to the contralateral lung or contralateral breast either with the FB or DIBH position between IMRT and VMAT techniques.

Discussion

Numerous retrospective planning and comparative dosimetric studies have demonstrated an important and statistically significant dose reduction to the heart and coronary arteries by using the DIBH position during left-sided breast irradiation with or without regional nodal irradiation [22–30]. This study is one of the larger series to evaluate the differences in dose reduction to OAR using the DIBH position and at the same time making a comparison between IMRT and VMAT irradiation techniques of left-sided breast cancer without regional nodal irradiation. After analyzing the extracted different doses from the DVH and comparing between the DIBH and FB position for each IMRT and VMAT plan, we found that DIBH irradiation resulted in a significant dose reduction of the heart and LADCA dose. Moreover, with IMRT, an additional significant further dose reduction could be achieved in FB and DIBH irradiation when compared with the VMAT plans (Figs. 5 and 6).

Is there any evidence for a clinical benefit of dose reduction to the heart and coronary arteries?

As of today there are no prospective studies or data available demonstrating a possible clinical benefit of DIBH irradiation on the late cardiac toxicity rate for left breast irradiation. Recently, preliminary retrospective data on CT-based calcium scores of the coronary arteries provided some evidence that radiation of left-sided breast cancer using breath-hold may be associated with less calcification [31, 32]. As it is clearly a late toxicity, collecting this data presumably needs many years to be available to assess the clinical impact of DIBH on cardiac toxicity. Even though the best clinical practice is to reduce the heart and LAD dose to as low as reasonably achievable, data from major retrospective series indicated that an increasing mean cardiac dose was clearly associated with a proportional increase in the rate of major coronary events. Sardaro et al. reported a 4% increase in the late heart disease risk per 1 Gy in mean heart dose [33]. Darby et al. have estimated that a 1 Gy increase in mean heart dose will result in a 7.4% higher rate of major coronary events, defined as myocardial infarction and death from ischemic heart disease [7]. Obviously, mean heart dose sufficiently reflected coronary artery exposure in patients treated with DIBH in a recent analysis [34, 35]. The current study showed a significant reduction in mean heart dose of 20% with IMRT and 23% with VMAT. Therefore, it has been ongoing and continuing institutional policy to use the DIBH technique whenever feasible since March 2014 as the standard irradiation method for all left-sided breast cancer patients in order to keep the heart and LAD dose as low as possible.

Radiation pneumonitis after breast irradiation is an uncommon, albeit severe, toxicity, and its rate of incidence

Fig. 5 Dose volume histograms of the heart displaying the typical dose pattern in a representative patient with left-sided breast cancer (1 DIBH-IMRT, 2 FB-IMRT, 3 DIBH-VMAT, 4 FB-VMAT)

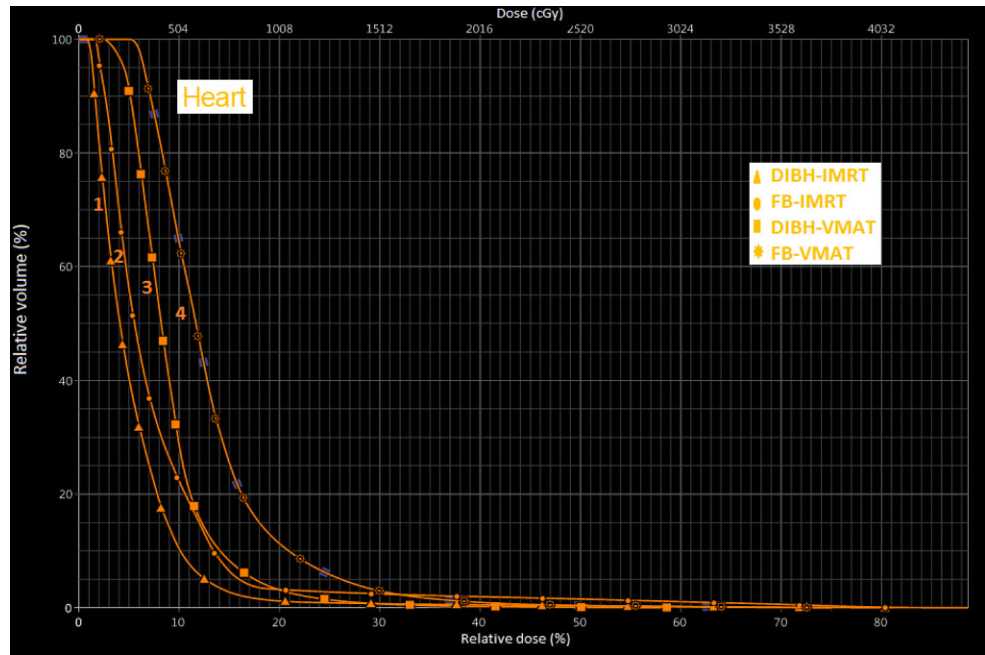
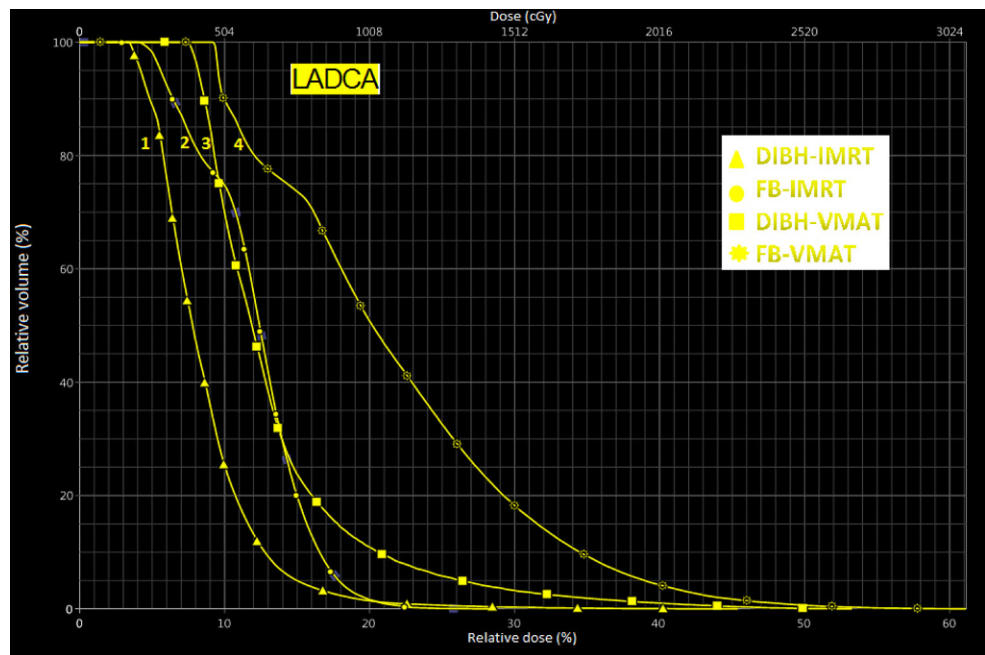


Fig. 6 Dose volume histograms of the LADCA in a representative patient with left-sided breast cancer (1 DIBH-IMRT, 2 FB-IMRT, 3 DIBH-VMAT, 4 FB-VMAT)



is correlated with the irradiated lung volume and radiation dose. Many studies indicated that the mean lung dose can be used as a predicting risk factor of radiation pneumonitis in breast cancer patients [22, 23]. Zürl et al. showed a 15% reduction (statistically significant) in the mean dose to the ipsilateral lung in DIBH versus FB in 60 breast cancer patients that were irradiated using an optimized tangential-field technique, as well as a 17% reduction (statistically significant) in the mean lung mass in the restricted area receiving ≤ 20 Gy [24]. Other planning studies have reported contradictory findings regarding the impact of DIBH irra-

diation on ipsilateral and contralateral lung dose [25–28, 33]. This study showed a slightly reduced mean dose to the left and right lung in DIBH irradiation, but this was only statistically significant with VMAT. This could be due to the small patient number in this study; larger studies are required to evaluate a possible difference between FB and DIBH irradiation, as well as between IMRT and VMAT techniques.

Ionizing radiation exposure is a known risk factor for breast cancer; this was particularly evident among women that were irradiated to the chest area for Hodgkin’s dis-

ease. This risk was estimated to be between three and seven times higher compared with female patients without radiation therapy [36]. In order to avoid the risk of radiation-induced contralateral breast cancer, it is important to minimize the contralateral breast dose. After analyzing and comparing 400 treatment plans with tangential fields in the DIBH and FB positions in 200 left-sided breast cancer patients, Zürl et al. reported a slight but significantly higher contralateral breast dose in the DIBH position compared with FB (0.69 Gy and 0.65 Gy respectively, $p = 0.01$). Increased contralateral breast dose in the DIBH position was mainly due to the shift in the medial field margin and theoretically associated with a higher risk of contralateral breast cancer among women aged ≤ 45 years (0.65 vs 0.61, $p = 0.001$, for DIBH and FB respectively) [37]. In the current study, the mean dose to the contralateral breast in DIBH irradiation was significantly reduced with VMAT planning, but not with IMRT compared to the FB position. Interestingly, second cancer risk may additionally be reduced using newer radiation techniques such as flattening filter-free mode of the linear accelerator, as has been reported recently [38, 39].

Conclusion

Left-sided breast irradiation is best performed in the DIBH position, since a considerable dose sparing to the heart and LADCA can be achieved by using either IMRT or VMAT techniques. IMRT planning enables a significant additional decrease in heart and LADCA dose compared with VMAT in both FB and DIBH irradiation. A slight reduction in mean dose to the ipsilateral and contralateral lung was seen with DIBH as compared with FB irradiation, being statistically significant only with VMAT.

Acknowledgements The present work was carried out by M.S. in fulfillment of the requirements for obtaining the degree “Dr. med.” awarded by the Friedrich Alexander University of Erlangen-Nürnberg (FAU), 91054 Erlangen, Germany.

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